

Appendix 1 Details of included studies.

Author	Country	Period of Study	Setting	Study Method	Number of patients	Outcome 1 ADR rate	Outcome 2	Outcome 3	Costs	Main drugs involved	Comments
Bates 1993	Boston USA	37 days, Aug- Sep 1990	Seven units at Brigham & Women's Hospital inc CCU	1. Nurse & pharmacist reporting; 2. Nurse investigator ward visits 2x daily weekdays; 3. Nurse investigator daily chart review. Prospective	420	27 ADEs and 34 potential ADEs for 2967 pt days (14.5% of admissions)	CCU 33ADE/1000 pt days, Medical 13/1000pt days, Surgical 7/1000, Obstetric 0/1000	19% life threatening, 33% serious. Overall 6 ADEs per 100 admissions	No estimates	Antibiotics 25%, cardiac 14%, anticoagulant 11%	
Bates 1995	Boston USA	Oct- Nov 1992 51 days.	Adults admitted to urban tertiary hospital 3 medical units	Prospective evaluation of new drug orders (medication errors): 1. Pharmacists at dispensing stage; 2. study nurse reviewed all charts; 3. trained reviewer checked all charts sent to pharmacy.	379	379 admissions. 10704 patient days. 530 medication errors for 10,070 orders. 1.4 medication errors per admission. 5.3 medication errors per 100 orders 25 ADEs in total noted. 5/530 resulted in an ADR.		For ADEs (n=25): 0% deaths, 1 (4%) life threatening, 7 (28%) serious, 17 (68%) significant	No estimates	Medication errors: Antibiotics 19%, electrolyte concentrates 10%, cardiovascular 8%, analgesics 7%	Describes medication errors more than ADRs
Bates 1995	Boston, USA	6 months, Feb to July 1993	All adults at two tertiary hospitals (11 units) inc medical and surgical ICUs (3 months each)	1. Nurse & pharmacist reporting; 2. Nurse investigator ward visits 2x daily weekdays; 3. Nurse investigator daily chart review. Prospective	4031	247 ADEs/4031 admissions (28% preventable). 194 potential ADEs 21,412 pt days total. Overall incidence 11%	6.5 ADEs per 100 admissions (adjusted rate). 11.5 ADEs /1000 pt days	1%ADEs fatal (none preventable) 12% life threatening, 30% serious, 57% significant 42% of life threatening and serious were preventable	Quote \$2000 per ADR from another source	Analgesics (73; 30%) (often infusion or PCA errors), antibiotics (59; 29%) sedatives (20; 8%), antineoplastics (18; 7%), cardiovascular (9; 4%), anticoagulants (8; 3%)	Second paper (Leape 1995) analyses the systems failures for the same study.
Bates 1997	Boston USA	6 months, Feb to July 1993	2 tertiary hospitals (11 medical and surgical units)	1. Nurse & pharmacist reporting; 2. Nurse investigator ward visits 2x daily weekdays; 3. Nurse investigator daily chart review. Prospective	4108	247 ADEs for 207 admissions	Additional in-patient stay of 2.2 days for ADR patients costing \$3244 per pt	No data	Estimated one yr. costs for hospital of \$5.6 million equiv. to \$8000 per bed per year. £1320 per bed per year	Warfarin, prednisone, cytostatics, theophylline.	Cases: patients with an ADE. Controls: pt on the same unit as the 'case' with the most similar pre-event length of stay. Incidence data duplicated in Bates 1995, cost data is additional
Bergman 1981	Sweden	3.5 months	Internal medicine dept	Prospective study 1. Pt interview by trained nurse or author on admission day for info on previous drug treatment. 2. Extra info from referral notes, case reports, family, home aids	285	16/285 patients admitted because of ADRs (5.6%)					Only definite or probable ADRs included. ADRs more likely in women & patients taking ≥4 drugs
Bigby 1987	Boston, USA	1983-84	Emergency admissions of patients from hospital based primary care practice.	Emergency admissions identified and standardised questionnaire used to judge preventability of admission. Prospective study	457		10.30% 24 preventable admissions due to ADR				
Black 1984	Perth, Australia	12 months, Jan-Dec 1979 - all inpatients.	8 general medical units.	Study of patient discharge summaries excluding deliberate self poisoning. Also Medical records dept figures for hospital admissions in 1977 classified by ICD codes (1523 patient days) were examined. Prospective study	481	Inpatient discharge summaries: 30/481 admissions (6.2%); 13 (2.7%) admissions definitely / probably drug-related; 17 (3.5%) possibly drug-related.	Medical Records Dept figures: Ave 7 days hospital stay			In-patient discharge summaries: 14/30 due to anti-inflammatory drugs - cardiac failure with phenylbutazone, gi bleeding /ulcer with aspirin & NSAIDs.	
Bowman 1996	Indianapolis USA	4 months	Internal medicine wards at 350 bed county general hospital	Chart review by clinical pharmacists. Prospective study	1024	237/1024 (23%)		304 ADRs/1024 patients.		Medical Records Dept - cardiac tonics, hydantoin derivatives, anti-diabetic drugs, anticoagulants	
Brennan1989	Boston USA	3 years Jan 84 to May 87	2 teaching hospitals in Boston	Retrospective chart review of 360 medical records. Validity testing of a two stage process to identify ADRs		No data		No data	No data	No data	Methodology paper
Brennan 1990	Boston USA	3 years Jan 84 to May 87	2 teaching hospitals in Boston	Assessment of validity of medical record review as means to identify ADRs. Litigation		No data		No data	No data	No data	Cases: patients with an ADE resulting in a law suit or risk management follow-up. Controls: patients of similar stay in hospital with no record of above.
Brennan 1991	New York State, USA	Admissions in 1984	51 randomly selected acute care, non psychiatric hospitals in NY State	Retrospective screening of records by nurses and medical records analysts, then 2nd stage by 2 physicians for identified records	30121	ADRs 3.7% (3.2-4.2) ADRs due to negligence 1% (0.8-1.2)	13.6% ADRs led to death, 2.6% led to total disability	Persons over 65 had double risk of ADR vs. 16-44yrs. No sig difference for gender	No data		
Caradoc-Davies 1987	Dunedin NZ	4 months in 1984	Geriatric Assessment and rehabilitation unit	Prospective study, assessment on admission and on discharge	205	27/205 (13%)					
Caranasos 1974	Florida USA	3 years Aug 69 to July72	Medical admissions	patients were identified as having drug related admission by a pharmacist who then interviewed the admitting clinician. Prospective study	6063	177/6063 (ADRad2.9%) admissions	11 (6.2%) deaths; 116 (65.6%) severe; 50 (28%) moderate.	Greater risk in 71-81 age group, white females at greater risk (both sig difference)	No data	109 separate drugs implicated. Non-narcotic analgesics 34; antibiotics 33, cardiovascular 28, cytostatics 34, diuretics 24, anticoagulants 16	
Carbonin 1991	Italy	4 months May-June & Nov- Dec 1988	22 medical & 19 geriatric units	Prospective study: 1. Daily ward visit by study physician - asked nurses/physicians to get info on possible ADRs. 2. Medical/nursing records reviewed	9148	532/9148 (5.8%) admissions. 532 definite or probably related to drug.	Severe: 312/532 (58.6%)	Probable or definite ADRs related to 1 drug (420 cases), 2 drugs (90 cases), ≥3 drugs (22 cases)	No data	Colchicine, salbutamol, antibiotics, diclofenac, nifedipine, furosemide, nitroglycerin, digoxin	Mean age 67 yrs. Hospital stay 18.1 days. Digoxin & derivatives were most frequently prescribed drugs, then ranitidine & nifedipine

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Chan 1992	Hong Kong	Mar to Nov 1990	Consecutive acute admissions to 2 medical wards	Prospective study. Review of hospital record followed by discussion with physician responsible for pt. Also interviews with pt	1701	ADRAd 74/1701 (4.4%)	Slight female predominance for ADR	ADRs greater in over 60 yrs		Sulphonylurea (22), NSAIDs (13), insulin (10), diuretics (8)	
Chan 1995	Hong Kong	4 months Nov 92 to Feb 93	Consecutive acute admissions to 2 medical wards	Prospective study. Review of hospital record followed by discussion with physician responsible for pt.	925	ADRAd 57/925 (6.1%)	Slight female predominance for ADR	6.1% admissions to this unit due to ADR		NSAIDs (16), sulphonylureas (11), diuretics (7), aspirin (7)	ADRs to Chinese herbal medicine excluded
Classen 1997	Utah USA	3 years Jan 90 to Dec 93	520 bed teaching hospital	Prospective case control study (Cases: patients admitted to hospital and reported an ADE. Controls: patients admitted to hospital but with no ADE).	91574	2227/91574 admissions (patients) ADRin 2.4%			Additional in patient stay of 1.94 days (Cost \$203) but for severe ADR 3.6 days	Opiates, digoxin, paracetamol, antibiotics, warfarin	Average number of drugs given to patient before experiencing an ADR was 12.52. See Evans1994
Col 1990	Massachusetts USA	3 months 1987	335 community teaching hospital Massachusetts USA. Elderly patients (65-99 yrs)	Interviews with patients. Prospective study	315	17% (ADRAd) admissions related to ADRs Total 315 admissions			\$4245 per hospital admission caused by ADR	Warfarin, prednisone, cytostatics, theophylline.	Also data on compliance. Non compliance related admission costs \$2150
Colt 1989	USA	6 months 1986-7	471 bed teaching community hospital	Retrospective chart review for drug induced illness	244	9.4% admissions drug related. 11.6% for over 65, 5.6% for under 65	Mean of 6.3 medications in group with ADRs vs 3.8 medications in group with no ADR			Aspirin and NSAIDs (61%), Cardiovascular (39%)	
Consentino 1996	Varese Italy	1 year	55 female psychiatric patients (long stay)	Regular prescription review and surveys recorded on database. Prospective study	55	8/55 patients experienced confirmed ADR				Anti-psychotics and hypoglycaemics	
Cooke 1985	Durban S.Africa	3 months 1982	150 white males and 150 white females consecutive admissions on two general medical wards in Durban	Prospective study looking for ADRs and deliberate self poisoning	300	14/300 admissions ADRs. ADRAd 4.6%; 29/300 self poisoning	Average stay of 8.3 days for ADR patients			Drugs with low therapeutic indices, digoxin, anti-coagulants	29/300 (9.6%) admissions for self poisoning Drugs: tranquillisers/ antidepressants,
Courtman 1995	Toronto Canada	5 months 1992	150 consecutive admissions on medical ward with geriatric admissions all patients reported over 65yrs	Pharmacist chart review for 5 drug related problems including ADRs. Prospective study	150	16/150 admissions	Patients on greater no of drugs had more drug related problems (p=0.0003)			NSAIDs (5), digoxin(3) lithium (2)	
Cullen 1997	USA	6 months 1993 (Feb - July)	4031 patients in 11 ICU and critical care units in 2 tertiary care hospitals	Units were randomly selected. 1. Reporting of incidents to nurse investigator. 2. Nurse investigator visited each unit & reviewed charts daily. Prospective study		In ICUs: 10 events per 1000 patient days (almost twice the rate for non-ICUs).	Length of stay: ICU 13 days, non-ICU 11.4	Av. 18% life-threatening, 44% serious, 38% clinically important	Costs in US\$ (thousands): ICU 19.7, non-ICU 14	Antibiotics, anticoagulants, cardiovascular, analgesics, antihypertensives, peptic ulcer drugs	Duplicate of Bates 1995
Cunningham 1997	Tayside Scotland	9 months March-Dec 92	Wards admitting elderly patients (>65 yrs).	Prospective study: Clinical pharmacist screening and compliance assessment	1011	144/1011 (14.2%) admissions (182 ADRs); 61% female; mean age 78 yrs.	54/1011 (5.3%) admissions definitely or probably drug related	64/182 (35%) preventable; 90/182 (49%) possibly preventable; 28/182 (15%) not preventable	No data	NSAIDs (15), steroids (5) opiates (4), anti-parkinson drugs (4) diuretics (3) nitrates (3), beta-blockers (2)	Phase II: 11/95 admissions definite or probable cases of overdose
Danielson 1982	NZ, Scotland and USA	4 years approx.	Surgical patients on selected wards in 5 hospitals	Prospective study. Nurse monitors and patient interviews	5232	1150/46868 drugs administered caused an ADR (2.5%)	42/5232 patients had serious ADR (0.8%) 20/5232 patients had life threatening ADRs (0.4%)	2.5% of drugs administered caused ADR, majority minor or moderate		Diuretics (12) warfarin (7), antibiotics (71)	
Dartnell 1996	Australia	30 days Nov-Dec 94	Emergency department tertiary hospital	Prospective study. Registrar and pharmacist reported followed by review	965	55/965 (5.7%) admissions were drug related. Female 62% Median age 58 yrs	4 (0.4%) deaths, 4 (0.4%) 3/55 (5%) definitely avoidable; 33/55 (60%) (0.2%) blood transfusion, 5 (0.5%) surgery	4 (0.4%) admissions to ITU, 2 (0.2%) probably avoidable; 19/55 (35%) unavoidable	£1.366m extrapolated to 12 months for DRAs	Antihypertensives (10); diuretics (7); corticosteroids (6); NSAIDs (5) anticonvulsants (5); cytostatics (5); cardiac (5); asthma (5); antithrombotics (5)	Cases of overdose were excluded
Denning 1996	California USA	One month (October ) 1994	Emergency department tertiary hospital	Pharmacist review of patient logs(retrospective)	1260	49/1260 had a drug related illness	8/49 drug related illness required admission		Cost of visit to ED for DRI \$696, Cost to institution 4400K per annum	No clear	Some of the drug related illnesses were linked to non-compliance
Dharmidharka 1993	Mumbai India	6 months 1989/90	Paediatric ward	Prospective comparative study, physician assessment vs. voluntary reporting	347	6/347 (1.7%), comparison group 1/363				Anti TB drugs	
el Baghir 1997	Abha, Saudi Arabia	2 years	Patients admitted to medical ward with either overdose or ADR	Examination of pre-selected group of patients. Prospective study	56	No evaluable data				NSAIDs, warfarin, anti TB drugs	
Evans 1994	Utah USA	31 months 1990- 92	520 bed teaching hospital	Case control		1348/60386 admissions	Additional in-patient stay of 1.94 days for ADR patients costing \$1939 per patient	Estimated one yr. costs for hospital of \$1,103,291 equiv. year to \$2100 per bed per year	£5000 per bed per	Not mentioned	Similar to data in Classen paper
Evans 1994	Utah USA	44 months 89-92	520 bed teaching hospital 79K patients	Computer printout scanned	79719	1865/79719 (2.3%) admissions		Reduced the incidence of type B reactions from 41 during 113K patient days to 12 during 103K patient days	No data		Uses Naranjo method Calculated on Type A reactions (action related) and B (idiosyncratic)
Frisk 1977	USA	Admissions screened by pharmacists	2 county medical units		442	No evaluable data					
Garcia- Martin 1997	Spain	One year 1993	Tertiary care hospital. 800 beds	Prospective study: Paired case control investigating deaths associated with ADRs		24% deaths related to an adverse event			No data		Data needs careful interpretation
George 1980	Southampton UK	Not stated	250 consecutive admissions to medical unit	Prospective study other details not stated	250	ADRAd 43/250 (17%), ADRin 6/250 (2.4%)					

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Gharaibeh 1998	Amman Jordan	18 months	All admissions from emergency and outpatient depts	Prospective study. Chart review followed by detailed history and patient examination and/or interview by clinical pharmacologist	6569	237/6569(3.6%) stated to be drug induced admissions.	45%severe, 1.5% fatal			Chemotherapeutic agents (36%), CNS (15%), hypoglycaemic(7%), anticoagulants (3%),	
Ghose 1980	Carlisle UK	3 months 1979	Admissions	Prospective study: patients checked for primary cause of admission	171	15/171(9%) drug related (not self poisoning)	Mean duration of stay for drug related was 8 days but not clear what this relates to				
Gosney 1984	UK	One month Jan 1983	General medical & geriatric wards - elderly patients (>65 yrs)	Prospective study. Case-records and prescription charts reviewed on admission, daily and on discharge. 604 patients >65 yrs (238 men, 366 women). 573 followed up.	573	136/573 (24%) patients given contraindicated or interacting drugs. 200 contraindicated or interacting drugs in 6160 prescriptions (error rate 3.2%)	Contraindicated drugs - 60 (0.97%) prescriptions. 52 potentially dangerous prescriptions (2.16%)	Adversely interacting drugs - No data 133 (2.16%) prescriptions. 9 potentially life-threatening, 51 likely to produce potentially serious side-effects, 41 clinically important & included in BNF		Digoxin, anticoagulants, diuretics	Number of drugs on arrival average 2.14, during hospital stay 5.48, on discharge 3.47
Gray SL 1999	USA	Not stated - part of larger study running from April 1994-May 1996	3 home health agencies, Wisconsin	Prospective cohort study. Interviews 1 month after discharge. 265 patients >64 yrs	256	Self-reported ADEs during the month following hospital discharge. 20.3% patients reported 64 ADEs	1/64 ADE led to hospitalisation	Female gender and new scheduled medications at hospital discharge significantly associated with ADEs	No data	Cardiovascular, antibiotics, CNS, endocrine, analgesics	Part of a larger cohort study - not referenced
Grymonpre 1988	Winnipeg, Canada	4 months 1983	Survey of drug related admissions in over 50 age group admitted to a primary care hospital	Prospective study. All patients screened to identify drug related admissions and data collected by clinical pharmacist	718	83/718 (12%)	Drug related problems occurred in 23% of patients on prescribed medications.	Strong association between number of drugs taken and number of ADRs		Beta blockers, steroids, digoxin, diuretics, NSAIDs	
Hallas J 1992	Odense, Denmark	15 months Mar 88-May 89	6 medical depts in University hospital	Prospective study. Drug histories 2-4 days post admission	1999	ADR contributing to admission 157/1999 (7.9%)	ADRs seen in patients on higher no of drugs, female dominance and older age (60+)	Calculates ADRs per one million DDDs for several drugs	No data	Anti-rheumatics & analgesics 27%, CV drugs 23%, psychotropic 14%, anti-diabetics 12%, antibiotics 7%, steroids 5%	
Hallas J 1990	Odense, Denmark	333 consecutive patients admitted to a medical ward over 2 months Mar-May 1988	Medical ward	Prospective study. Drug histories 2-4 days post admission		63/286 experienced either ADR or drug treatment failure	ADRs seen in patients on higher no of drugs, female dominance and older age (60+)		No data		Data part of that published in Hallas 1992
Hardman1986	Lincoln UK	5 weeks	Acute beds	Prospective study. Pharmacist prescription review	300	69 ADRs recorded					
Harte 1980	Republic of Ireland	4 months approx.	Paediatric wards from 5 hospitals	Prospective study: data recording forms sent by pharmacists to hospitals	469	37 ADRs recorded (4.2%)					Assumes prescriptions refers to items
Hurwitz 1969	Belfast UK	12 months (65-66)	Wards of 2 Belfast hospitals	Prospective study using interviews, examination of notes and observation			Older patients (over 60), women have sig more ADRs	patients with 6 or more drugs significantly more ADRs. Previous experience of an ADR also significant		No data	See other papers on same data
Hurwitz 1969	Belfast UK	12 months (65-66)	Wards of 2 Belfast hospitals	Prospective study using interviews, examination of notes and observation	1268	2.9% admissions due to ADR and 2.1% for self poisoning . Total admissions 1268				No data	See other papers on same data
Hurwitz & Wade 1969	Belfast UK	12 months (65-66)	Wards of 2 Belfast hospitals	Prospective study using interviews, examination of notes and observation	1160	118/1160 (10.2%) experienced and ADR during in-patient stay	55 reactions occurred on the first day of treatment, 16 within one hour of administration		No data	Cardiac glycosides, antibiotics , bronchodilators	Comparative table with 8 other surveys in commentary. See other papers on same data
Ibanez 1991	Barcelona Spain	723 days intermittent over 3 yr. period	Selected diagnoses for patients admitted to medical and surgical wards.	Review of admission diagnoses reviewed intermittently. Review of records looking for possible ADRs followed by patient interview	7728	554/7728 (7.2%)					Unreliable data as only sub group analysed
Ives T 1987	N. Carolina USA	12 months	Admissions to family medicine inpatient services. No neonates included.	Retrospective review of notes by physician or clinical pharmacist	293	17/293 admissions were due to ADR (5.8%)	Main outcome is drug related admission. Patients with DRAs tended to be older mean 59yrs. Highest risk in 60s & 80s	Widowed patients had higher incidence of ADRs		No data	Small numbers of participants
Jacubait 1990	Heidelberg, Germany	Data collected from 1980 to 1987	All hospitalised patients	retrospective analysis	70407	13749/70407 (17.9%) ADAad 1.6%	ADRs much higher in over 60s (three times greater than in under 20s)	ADRs greater in females			
Klein 1976	Bern Switzerland	One year 1972	Medical service admissions	Prospective study. Monitoring system on admission	914	171/914 admissions due to ADR (18.7%)	6.8% of ADRs are life threatening		No data	Chemotherapeutic agents (29.5%), digitals preparations (23%), anticoagulants (10%), other cardiovascular agents /diuretics (6%), analgesics (6%)	
Lakshmanan 1986	Cleveland USA	Two months (July & Aug) 1984	All medical service admissions	Prospective study. Admissions monitored to identify all iatrogenic admissions caused by medicines, surgery or diagnostic procedures	834	45/834 (5.4%) iatrogenic admissions. 35 drug related; 9 procedure	2 severe, 81 moderate	No significant difference between iatrogenic group and control in terms of age, length of stay, number of drugs. Iatrogenic admissions had 0.83 more diagnoses than control	No data	Antihypertensives (8); physiological modulators (7) cytostatics (6); diabetes (5);	

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Lapeyre-Mestre 1997	Toulouse France	One year 1993	Cancer chemotherapy patients	Retrospective trawl of hospital standardised medical outcome summary and ICD9 codes	3429	171/3429 patients (5%) , 60.2% female. Mean 51 yrs	182 serious ADRs in 106 patients. 20% dubious, 68% possible, 12% likely		380 for 12 months	Antineoplastic agents.	Only 15 ADRs reported by traditional methods during same period
Larmour 1991	Melbourne Australia	6 months 1987	407 bed teaching hospital	Prospective study, pharmacist interviews on admission. Twice daily check of drug charts	5623	90/5623 admissions were ADR related (1.6%). 53% of patients with ADR were 70 or older (this category was only 24% of Hospital Popn)	5/84 died as result of ADR	27 drug interactions noted	20 patients costed A\$110,000. Approx. £2750 per pt	NSAIDs, cardiovascular drugs, digoxin, warfarin	40 (0.7%) admissions due to overdose or accidental poisoning
Leach 1986	Barnsley UK	5 months 1985-86	Consecutive patients to acute geriatric unit.	Prospective study. Observer interviews using proforma	521	94/521 (18%)		117adrs in 94 patients		Antibiotics, diuretics, sedatives, potassium, digoxin	
Leape 1995	Boston USA	6 months Feb-July 1993	All non obstetric adult patients at Brigham & Women's and Massachusetts General- units	Daily ward visits by trained nurse investigators to get verbal reports followed by relevant review of patients notes		Looked at systems causing ADRs and ranked them. Lack of knowledge of the drug or lack of knowledge of the patient were most significant			No data	No data	See Bates 1995 for results
Leape 1991	New York State, USA	Records examined in 1984	30,195 records randomly selected from 51 hospitals	Retrospective screening of hospital record by trained nurses/ administrators. Those selected then reviewed independently by two clinicians.		178/30195 (0.6%)	Elderly (>64 yrs) were twice as likely to have an ADE		No data	No data	Link to Brennan & Leape 1991
Leape 1999	Boston USA	2 blocks: 1st stage: (6 months Feb-July 1993). 2nd stage (9 months Oct 94-July 1995).	2 medical ICUs in Massachusetts, & 1 tertiary care hospital in Boston. Randomly selected 75 patients plus 50 from control units (15 bed CCU).	Prospective study. Daily pharmacist review of medical records (including medication orders). Incidents evaluated by 2 physicians.	75	66% reduction in rate of preventable ADEs at ordering stage (1st to 2nd stage) with pharmacist participation: 10.4 (95% CI 7-14) to 3.5 (1-5) per 1000 patient-days.			Quote \$2000 per ADE [Bates, 1997; Classen, 1997]	No data	See Leape 1995
Levy1973	Israel & N America, including Canada. Boston Collaborative Drug Surveillance Program (BCDSP)	Seven years: 1969-1972	Medical departments in Israeli & N American hospitals	Prospective study: 1. Monitor (nurse or pharmacist) extracts data from clinical records, interviews patient and clinician 2. Clinician asked about ADRs. 3. Team from BCDSP decide if ADRs are drug related 4. BCDSP reports assessed for correctness	11891	21.6%ADR rate. 6.7% ADRin, 27/6199 deaths due to ADRs. ADRs occurred in 28% patients in Israel (9% of drug exposures) and 27% patients in N America (5%)	Israel - 6.2% major severity, 1.9% life-threatening, N America - 11.3% major, 4.5% life-threatening	Hospitalisation due to ADRs: No data Israel - 73/1239 (5.9%) patients N America - 797/11891 (6.7%) patients Total - 870/13130 (6.6%) patients		Israel: ACTH, hydralazine, cephalothin sodium, nitrofurantoin, prednisone, heparin. N America: Not stated	Ave number of drugs per patient 6.3 Israel, 8.8 N America. Hospitalisation prolonged in 1.8% & 1.9% Israeli & N American patients respectively
Levy 1977	Israel	Eight years 1969-76		From Levy 1973:		ADR rate 14.5%					
Levy1979	Israel			Subset of Levy 1977		ADRad 4.1%					
Levy 1980	Israel and Germany. Only German data used	1974-77	Admissions to clinical pharmacology unit Berlin	As Levy 1973	2933	ADRad 5.7%					
Levy 1999	Jerusalem Israel	2 months	34 bed medical ward	Study to determine if signals from laboratory on patients clinical chemistry can highlight ADRs not picked up by clinicians		65/199patients (32%) had adrs					See Tegedor
Lucas 1991	Oregon USA	Commentary only. No evaluable data									Useful introduction to ADR terminology and background
Mackay 1987	Kaitala, New Zealand	1983	Medical ward	Retrospective review of patient notes	429	50/429 (12%) excludes ODs	Extrapolation leads to 14000 admissions in NZ for drug induced illness			Digoxin, sedatives, beta-blockers, NSAIDs	66 drug induced admissions of which 16 were deliberate overdose
Maistrello 1995	Milan, Italy	12 months	Medical ward	Prospective study. Drug surveillance program (ARIES) and algorithm. Random independent evaluation of reports	1203	Actual 7.4%	Review of 105 of the patients notes suggest an under-reporting but not clear by how much				
Major 1998	Beirut, Lebanon	6 months	Admissions to medical and paediatric services	Questionnaire including detailed history. Prospective study	2202	122/1745 (7%)	Children: 26/457 ADRs (5.7%)		Estimated at 10% health care costs and 10% admissions caused by drug related hospitalisation	NSAIDs 22%, chemotherapy 21%, CVS 17%, metabolic and endocrine 8%	
Manesse 1997	Rotterdam, Netherlands	3 months, Feb-May 1994.	All admissions of patients aged 70 or over to medical wards in single hospital.	Prospective study using history, examination, lab tests and patient interviews.	106	128/533 admissions identified for assessment. 100 patients evaluable. 56% female. Mean age 78	Drug-related deaths 0/106, severe reactions 25/106	Patients ability to identify a reaction was assessed. 28/93 correctly recognised an ADR & 45 its absence. 18/25 with a severe ADR could not implicate the drug.	No data	Diuretics (falls), anaemia due to GI bleed (NSAID) mentioned	Patients were receiving a mean of 5.9 drugs. Authors state that ADRs are related more to the number of drugs than the presence of more diagnoses.
Martinez -Mir 1996	Valencia Spain	Summer 105 days & winter 99 days	All children aged 2 or below admitted to 47 paediatric beds	Prospective study. Screening of hospital record using a structured questionnaire	490	21/490 (4.3%) admissions caused by ADR. 42 identified ADRs	Severe (8); moderate (12), mild (1).			Respiratory drugs (14), anti-infective (10), CNS drugs (6), dermatology drugs (4)	Patients were receiving a mean of 5.8 drugs. Antineoplastic drugs excluded from ADR assessments.

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May-77	Florida USA	June 1974 to Jan 1975	One neurological and two medical services	Pharmacists took medication histories on a proportion of patients admitted during the study period	1242	334 patients interviewed. 10.2% experienced an ADR during hospitalisation	9.3% either had ADR on admission or one led to admission	ADRs slightly higher among women, those who had previously experienced and ADR and those who stayed in hospital longer than 15 days. Black males had a lower ADR rate.			
McKenn 1976	Virginia USA	2 months 1974	110 bed general medical ward in large teaching hospital.	Prospective study. Pharmacist interview of all patients	216	24/216 (11.1%) patients experienced at least one ADR	17/216 (7.9%) admitted due to ADR. 4 had life-threatening ADRs; 34% definitely & 34% probably drug related	Average no of ADRs per pt is 1.3 (range not stated)	ADRs cost 590 hospital days and approx. \$60,000	Diuretics, digitalis, NSAIDs	Drug overdose: 4 (1.9%) admissions
Miller 1974	Boston USA	Boston Collaborative Drug surveillance programme April 69-Jan 72	Medical wards in 7 hospitals, 5 in Eastern USA, 1 in Canada, 1 in Israel.	Data collected on all consecutively admitted patients together with interviews		260/7017 (3.7%) admissions due to ADRs	35/7017 due to ADR of illicit substance, 51/7017 due to deliberate overdose.			Digoxin, NSAIDs, prednisone, warfarin.	51 (0.7%) admissions due to accidental or intentional overdose
Miller 1973	Boston USA	Data up to Jan 72 reported from surveillance program. Approx. 6 yrs (11,500 patients)	Medical wards in 7 hospitals, 5 in Eastern USA, 1 in Canada, 1 in Israel.	Data collected on all consecutively admitted patients together with interviews		Data based on drug exposures, and refers to administration of a drug. It is counted once per pt and is irrespective of dose, form, route etc.	Average number of drug exposures: 8.7 (6.3 - 9.7).. 3.3% of ADRs were life-threatening	5.5% (range 3.9-8.2) of drug exposures result in ADR		Heparin, prednisone, diuretics, digoxin, antibiotics	
Moore 1998	Le Havre, France	6 months	Internal medicine dept (29 beds)	Prospective study of all admissions with estimate of number admitted for drug related diagnosis or suffered ADR in hospital	329	31/329 (9.4%)	ADRad 3%, ADRin 6%	patients admitted for ADR were older, more often female and took more drugs.	Estimated cost per bed per year: £4673		
Nelson 1996	Texas USA	One month	Coronary and medical intensive care	Prospective study. Daily review of admissions by clinical pharmacist. Initially followed by interviews with pt but this discontinued after 1 week	450	24/450 (5.3%)	49% considered definitely avoidable			Hypoglycaemic agents, diuretics, antibiotics and CVS drugs	
Prince 1992	Pittsburgh USA	4 months 1990-1	All patients who visited the Emergency department of this 517 bed hospital	Retrospective study. Chart review by clinical pharmacist retrospectively except for admitted patients who were reviewed concurrently	10184	81/10184 ADR (0.8%)	14/81 required admission	Drug related illness constituted 2.9% of all admissions and the average cost was \$8888			
Raschetti 1999	Rome Italy	12 months but only the first week of each month	All patients who visited the Emergency department	Prospective study. Record of visits by nurse and retrieval of notes.	5497	235/5497 experienced an ADR (4.3%)	45/1833 admissions from ED for ADR (2.4%)	Mortality rate of 2.7 per 1000 admissions			
Salem 1984	USA	4 months	Veterans administration hospital	Prospective study. Interview 3 days after admission and follow up.	41	No evaluable data					
Scheinman-McIntire 1996	USA	1 year 92-93	Emergency Department in HMO	Prospective study. Evaluation of patient records within 3 weeks of admission	62216	ADRad 1%, visits to emergency department due to ADR 1.7%	62% female	Subgroup of those suffering ADR given telephone interview with pharmacist. Pt understanding of potential ADRs was poor		Anti-infectives (24%), analgesics(235), cardiovascular (18%), respiratory drugs (9%), hypoglycaemics (6%)	
Schimmel 1964	Connecticut USA	8 months August 1960 - March 1961	3 University hospital medical wards	Prospective study. Reports of within hospital ADRs. Patients admitted because of treatment related ADRs were excluded	1014	103/1014 (10%)	103 patients with 119 episodes related to drug therapy, 4 of these patients died		No data	Antimicrobials, hormone preparations (e.g. insulin, steroids, ACTH), Antineoplastic drugs, sedatives & tranquillisers, anticoagulants	Deaths - episodes were primary, precipitating or contributory factors
Schlienger 1998	Toronto Canada	Jan 90 to June 96	Patients admitted for or developing severe cutaneous or hypersensitivity reactions to antiepileptic drugs.	Prospective study. Medical records database search based on ICD9 codes	384	Selective reporting - no reliable data	8/13 admitted to hospital; median stay 9.5 days.		Median costs per ADR	All anticonvulsants: 8/13 phenytoin; 3/13 carbamazepine; 3/13 valproate	
Schlienger 1999	Basel, Switzerland	24 months	General medical wards covering infectious diseases, cardiovascular, haematological, oncological and peripheral vascular diseases.	Prospective, comparative, open, crossover study to evaluate the effect of a pharmacist on reporting and identifying ADRs	941	137/941 (14.6%) reported in test, 21/1018 (2.1%) reported in control	15.5 ADEs per 1000 pt days 0.0264 ADEs per drug prescribed				
Schneider 1995	Ohio USA	Retrospective chart review July 92 to June 94	All patients known to have had ADR or medication error	Retrospective chart review to determine cause and effect relationship		No evaluable data	17% ADRs considered avoidable		Est. \$783/per report		
Schoenemann 1998	Germany German language	12 months	Medical wards in a general hospital with gastroenterology focus	Prospective study using proforma	4032	315/4032 97.8%)	ADRad 101/4032 (2.5%)			NSAIDs, antibiotics and chemotherapeutic agents	
Shapiro 1971	USA	Not stated 6199 consecutive medical patients	Medical inpatients in 6 hospitals	Prospective study. Study of drug attributed deaths, surveillance of ADR reports and physician interviews.	6199	Drug related deaths due to ADR 0.44%. 27 deaths in 6199 patients				Potassium supplements, IV fluids, narcotics, antibiotics, anticoagulants.	Each case described in detail
Smith 1996	Oxford UK	3 years (April 1990 - March 1993)	1 hospital (7 acute general medical wards including 1 specialist gastroenterology ward)	Retrospective assessment of ADR reporting scheme	20695	1420 suspected ADRs /20695 admissions (6.9%)					2.3% of ADRs were for new drugs (all suspected ADRs)

Author	Country	Period of Study	Setting	Study Method	Number of patients	Outcome 1 ADR rate	Outcome 2	Outcome 3	Costs	Main drugs involved	Comments
Stanton 1994	Tasmania, Australia	10 weeks, March to August 1993	Four adult general medical wards	Review of admission diagnoses followed up with pharmacist interviews looking for drug related admissions (all causes)	691	3.1% admissions due to ADR				8/21 admissions due to gastrointestinal bleeding related to NSAIDs. Only one of these patients was taking anti-ulcer drugs	Figures for drug overdose also reported
Steel 1981	Boston USA	5 months	2 floors of a medical service at a teaching hospital	Retrospective chart review and data extraction supplemented with questioning of clinical personnel caring for the patient	815	290/815 (36%) experienced iatrogenic illness	76/815 major complications, 15/815 (2%) led to death				
Stewart 1980	Florida USA	6 months	Admissions to inpatient adult psychiatric service	Prospective monitoring of patient by primary investigator. Several drug related issues recorded, only adverse effects reported here	60	ADRad 3/60 (12%)		Five patients were admitted due to non-compliance.		Lithium and anticonvulsants mentioned in respect of ADRs	
Tegeder 1999	Erlangen, Germany	17 months	9 bed medical ward	Prospective study. Study to determine if signals from laboratory on patients clinical chemistry can highlight ADRs not picked up by clinicians	294		17/95 patients experienced ADRs that could have been detected by an abnormal lab test.	Only one third of ADRs detected and treated by clinicians			
Trunet 1980	Creteil France	1 year Aug 78-Aug 79	Multidisciplinary Intensive care unit	Prospective study. Patients admitted on alternative weeks were assessed for iatrogenic disease	325	41/325 (12.6%) admitted due to iatrogenic disease. 9/325 ADRs (2.7%)	14/325 (4.3%) due to therapeutic errors, 9 overdoses, 2 therapeutic antagonisms and 3 contra-indications	2.7% admissions to ICU due to ADRs. Caution small numbers		Numbers too small	
van den Bemt 1999	The Netherlands	2 months in 2 different hospitals in 1996 and 1997	Internal medicine inc paediatric and geriatric	Prospective study. Patient reports collected by Drs and nurses by direct question "did you experience an adverse drug reaction on the previous day?"	620	179/620 reported at least one ADR (29%)	Total no of ADRs was 311 Mean 1.7 adrs/pt range 1-10				
van Kraaij 1994	Netherlands	3 months	Admissions of patients over 65 years to two general medical wards.	Prospective study. Pt evaluation and probability using Naranjo algorithm	105	59/105 (56%)	120 different ADRs		No data	Diuretics, laxatives, antimicrobials	
Wang 1971	USA	1 year 1967-68	Veterans Administration Hospital, general medicine and surgery.	Prospective study. Nurse observer	8291	1.5% reported an ADR	Majority of ADRs were allergic reactions, rash, pruritis etc followed by gastro-intestinal, cardio-respiratory, neuromuscular and haematological.			Antibiotics (58%), contrast media(19%),	Population observed 99% male.
Warren 1994	USA	1 year 1987	Medicare population using digitalis	Retrospective study. Data trawl of Medicare records for patients with ICD9CM code for 'poisoning by cardiotonic glycosides' or adverse effect in therapeutic use of cardiotonic glycosides	8.53 persons hospitalised per 1000 persons using digitalis (estimated data)	12 persons hospitalised per 1000 persons using digitalis aged 85-99	Female rates higher (9.61) and black race (11.37)			Rationale for prescribing digitalis was unclear or weak in 73% of records examined.	
Williamson 1980	UK	Not specified	50 geriatric units asked to supply data on 50 consecutive patients admitted. 42 unit made returns	Prospective study. Pro-forma questionnaire	1998	248/1998(12.4%)	patients on one drug had ADR rate of 10% , on six drugs, 27% (p<0.001) ADRad 12%	ADRad 209/1998 (11%) 2/1998 died as result of ADR		Diuretics caused most ADRs, but commonly used in this group. Hypotensives, antiparkinsonian drugs psychotropics and digitalis all contributed greater than 10% of ADRs	Estimate 3900 geriatrics admitted annually solely for an ADR (2.8%)
Wilson 1995	New South Wales & S. Australia	1992	Private and public acute-care hospitals (31 hospitals, 500 records from each) chosen at random	Retrospective review of medical records by nurse, then independent review by 2 medical officers	14210	233/14210 ADRs drug related (1.64%)	2353/14655 = 16.6% (95% CI 15.2% to 17.9%) additional 7.1 days in hospital	AEs accounted for all adverse reactions all causes. 51% of AEs preventable. 4.9% of AEs resulted in death	No data	Antibiotics, cardiovascular, anticoagulants, antineoplastic, antihypertensive	
Wilson 1999	Re-examination of data presented in Wilson 1 (1995)										
Wu 1996	Taiwan	21 months 92-93	17 bed family medicine unit	Prospective study. Screening of all patients for drug related problems on admission and during stay. ADRs identified by clinician and confirmed by pharmacist	666	ADRad 23/666 (3.4%) ADRin 18/666 (2.7%)	33 ADRs (80%) were serious or moderate	Netilmicin, Atenolol, Cotrimoxazole, Chinese crude medicines caused serious ADRs		Antibiotics, cardiovascular, Chinese crude drugs, analgesics and NSAIDs	Chinese medicines implicated in causing chronic glomerulonephritis

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<b>Review articles and other related papers</b>											
Beard 1992		Review Article comments on pre-disposing factors									
Einarson 1993	Worldwide	Review - not relevant	Studies of ADR related admissions 1966 to 1989	Review article of 36 papers	2897/69187 admissions.	5% of admissions due to ADRs died. 25% patients who experienced ADR went on to experience a subsequent ADR.	No data	Drugs listed by study	10 papers same as included in Lazarou		
Griffin 1986	Worldwide	Not clear - historical overview of ADR monitoring	N/A	Survey of the ADR reporting scheme in 15 countries		Over 200 ADR reports per million of popln in 7 countries	Average of 2.5% ADRs related to fatality (range 0.4% to 10%) 29% of ADR reporting for NSAIDs	No data	Detailed lists of top 10 drugs producing ADRs by country and year. Co-trimoxazole appeared in all lists	?Use fatality data to define parameters	
Johnson 1995	Arizona USA	Not relevant	Telephone interviews with 15 'expert' pharmacists		23% (+/- 13%) would experience treatment failure, 10% (+/- 5%) would experience new medical problem, 6% (+/- 4%) would experience both	Drug related morbidity and mortality estimated at \$76.6 billion	Drug related hospitalisation est. to cost \$47 billion and cause 8.8 million admissions billion	Drug related admissions: £30 billion	No data		
Karch 1975	Not relevant	Not relevant	Mainly adult medical (12), psychiatric (2), surgical (2), all patients (1)	Critical review . Lists 12 studies from 1965 on			No data	No data		No search strategy or inclusion/exclusion criteria	
Lazarou 1998	Not relevant	Not relevant	Patients admitted to hospital or patients experiencing ADR in hospital over 32 yr. period in USA	Meta-analysis of 39 studies.	Serious ADRs 6.7% (5.2-8.2%). Fatal ADRs 0.32% (0.23-0.41%)	ADRin all severity's 10.9%. ADRad all severity's 15.1%	In 1994 in USA estimated 2.2 million patients had serious ADRs and 106 thousand had fatal ADRs. 4th to sixth leading cause of death in USA	No data		ADRad Admitted due to ADR; ADRin experienced ADR while in hospital 4 studies are included in Karch above	
Manesse 1989	Extract data Review article for terms and clinical pharmacy										
Moore 1998	USA	Commentary on ADR problems			States only 1% ADRs reported.	51% of drugs have ADRs not reported prior to					
Naranjo 1981	Toronto, Canada	Assessment tool for the probability of causal relationships for									
Neale 1998		Medico-legal: claims arising from the care of patients admitted as medical emergencies									
Rawlins 1988	UK	Description of spontaneous ADR reporting	No evaluable data								
Roughhead 1998	Australia	Review of 14 Australian studies some of which not readily available from standard	Review of literature with studies requested from authors that were identified by electronic and handsearching		2.4 to 3.6% of all admissions drug related						
Runciman 1998		Method of computerised recording of ADRs									
White 1999	Not relevant -economic overview		Economic review				Range of \$US 2262 to 3244 per ADE				